

EDITORIAL COMMENT

Myocardial Perfusion Imaging Using Ultrasound Contrast Agents

Now or Never?*

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Ultrasound contrast agents (UCAs) have been in the echocardiographic “toolbox” for many years. Two such agents (Definity [Lantheus Medical Imaging, North Billerica, Massachusetts] and Optison [GE Healthcare, Princeton, New Jersey]) are approved by the U.S. Food and Drug Administration (FDA) and are commercially available for left ventricular cavity opacification in patients with technically difficult echocardiograms. The greater, still unrealized value of these unique erythrocyte tracers, however, resides in their ability to depict the spatial distribution of myocardial perfusion and to quantify intramyocardial blood volume, properties that render UCAs ideal for the detection and localization of coronary artery disease (CAD).

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UCAs have had a checkered history, particularly with respect to myocardial perfusion imaging. The literature is replete with studies showing the promise of myocardial contrast echocardiography (MCE) for CAD detection (1,2). Studies in dogs dating back to the early 1980s hinted at the potential of UCAs for echocardiographic assessment of myocardial perfusion (3). Subsequent milestones included the development of second-generation UCAs capable of transpulmonary transit (1), placement of sophisticated UCA detection strategies on ultrasound imaging systems (4), and animal studies

proving the principle that MCE can measure intramyocardial blood volume and hence detect CAD during stress testing (5,6). In 1997, Kaul et al. (7) ushered in what was viewed by many to be a bright new era for MCE, demonstrating in humans the concordance between stress MCE and single-photon emission computed tomography images. This perception of a bright future was exemplified by a surge of publications in this area, alongside industry efforts to achieve FDA approval for new UCAs developed specifically for MCE (1,2).

Then, in October 2007, the FDA mandated product labeling revisions for Definity and Optison that included a “black box” warning that cited safety concerns, extended monitoring requirements for all patients, and new contraindications (8). Around this same time period, 2 companies (Point Biomedical Corp. [San Carlos, California] and Acusphere Inc. [Cambridge, Massachusetts]) with New Drug Applications for UCAs (Cardiosphere and Imagify, respectively) failed to receive FDA approval, with the execution of FDA recommendations for additional clinical trials proving to be financially insurmountable; currently, clinical trials to commercially develop UCAs for MCE have ceased in the U.S. Such events raised serious questions about the future of MCE.

Subsequent multicenter analyses of records reflecting >200,000 patients receiving UCAs confirmed their relative safety in a range of clinical settings (9–12). In July 2008, the FDA relaxed its relabeling mandate, reducing the monitoring requirements and narrowing the contraindications to UCAs (13). More recently, there seems to be renewed industry effort in pursuing approval of UCAs for the myocardial perfusion indication in Europe, and efforts in the U.S. have been initiated

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by another UCA manufacturer (Bracco Diagnostics, Milan, Italy) to pursue perfusion imaging—albeit of the liver—in radiologic indications.

Optimists might interpret these recent developments as the early markers of a resurgence of UCAs, which could even culminate in the clinical implementation of MCE. Against this historical backdrop, the study by Arnold et al. (14) in this issue of *JACC* is a timely contribution to what could be a reascendancy of MCE. This study evaluated the diagnostic accuracy of adenosine stress MCE in a small cohort of intermediate-risk patients scheduled for coronary angiography. The truth standard for coronary anatomy and physiology were cardiac catheterization and high field strength (3-T) perfusion cardiac magnetic resonance (CMR), respectively. Although it can be argued that CMR and MCE are inherently not comparable because the former uses a diffusible tracer (gadolinium), whereas the latter uses an intravascular probe, let us accept the premise of comparability. The diagnostic accuracy of MCE for angiographic $\geq 50\%$ coronary stenosis was 82%, with a respectable sensitivity of 85% and specificity of 76%, values that were statistically no different from those of CMR. Furthermore, MCE and CMR were comparable in diagnostic accuracy for identifying the extent and location of angiographic CAD. MCE had 85% sensitivity, 74% specificity, and 79% diagnostic accuracy for detection of CMR-defined inducible ischemia, and 87% diagnostic accuracy for detecting inducible ischemia on a per-vessel basis.

Of note, inducible ischemia was detected by CMR in 11% of segments, which was significantly higher than the 7% detected by MCE, suggesting that MCE may underestimate total ischemic burden. Whether this underestimation was more prevalent in particular vascular territories than others is not reported, nor is the concordance between CMR and MCE on a per-vessel or per-segment basis provided, likely because of small patient numbers. Also notable is that despite the good diagnostic accuracy of MCE for predicting angiographic disease on a per-patient basis, there was a strong trend for MCE to lag behind CMR in its sensitivity for detecting multivessel disease, although, conversely, its specificity exceeded that of CMR in this category. MCE might have performed better had the authors used flash-replenishment imaging because segmental differences in replenishment time could signal CAD despite apparently homogeneous peak videointensities (2). Also, despite efforts to create a patient cohort with an intermediate likelihood of

CAD based on the inclusion/exclusion criteria, the referral bias inherent in a study population undergoing cardiac catheterization should caution us in applying these data to populations with a lower pre-test probability of CAD.

Limitations notwithstanding, this study reasserts the potential of MCE to be a useful diagnostic tool. The study reminds us to consider whether the time may be ripe to relaunch a concerted effort to move MCE into the clinical arena. The landscape has changed, such that the time may be more auspicious than before for such an effort to take place, for at least 3 reasons. First, there is heightened concern about excess cancers resulting from exposure to nontrivial levels of ionizing radiation resulting from contemporary medical imaging practices, as recently outlined by the FDA (15) and others (16). Second, significant shortages in the radioisotope technetium-99m, which is used in 97% of patients undergoing nuclear stress testing, have recently developed due to the tenuous status of 2 (of only 5 worldwide) nuclear reactors that supply most of the world's molybdenum-99, the precursor of technetium-99m (17). Third, other promising indicators of MCE's possible turn-of-fortune include the revision of the FDA black box warning (13) and greater interaction between echocardiographers and the FDA, such that both parties are vastly more informed of each others' concerns than was previously the case. Additionally, as has always been true, MCE offers practical advantages of simpler instrumentation, less expense, and portability.

So, have the stars finally lined up for MCE's future? Is it “now or never” for MCE to make its big break into clinical practice? If the answers to these questions are “yes,” what will it take to move forward? Of course, an agent approved for MCE by the FDA should exist—a tall order that is, however, not impossible to achieve. But is that all there is to it? Unlikely. It is too easy to place blame on the FDA, industry, or reimbursement issues for the lack of clinical maturation of MCE. It should be noted that even when Definity or Optison are used for the FDA-approved and reimbursable indication of ventricular opacification, their concurrent, no-added-cost usage for perfusion imaging, albeit off label, has not been adopted by clinicians. Gadolinium-diethylenetriaminepentaacetic acid is not FDA approved for CMR perfusion imaging, yet ironically it was the gold standard in the present study, suggesting that FDA approval of UCAs, although important, is not the sole prerequisite to clinical adoption of MCE.

Beyond FDA approval, for MCE to “happen,” there needs to be buy-in by the clinicians themselves; we need to decide, as the community of imagers, whether to learn MCE imaging, much in the same way that clinicians make the conscious decision to train in coronary computed tomography angiography or CMR. It is naïve to think that high-quality MCE can be performed with the simple turn of a switch; there is a learning curve that must be traveled. Without the commitment of clinicians to learn and use MCE, it is unlikely that UCA companies will see value in expending resources to achieve FDA approval for myocardial perfusion imaging.

Despite the recent setbacks for UCAs and MCE, the study of Arnold et al. reminds us that MCE is

a technology with great clinical promise. It affirms what many of us who have used MCE in patients have observed for years: it works. This study alerts us that the time is propitious, perhaps more than ever before, to move MCE beyond proof of concept to a place where our patients can genuinely benefit from this imaging technology.

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